UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,045	04/06/2000	Brian Lee Sauer	OMRF 178	8128

23579 7590 02/26/2002

PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400

EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/544,045	Applicant(s) Sauer et al.
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 1, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above, claim(s) *50-63* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☒ The proposed drawing correction filed on *Oct 26, 2000* is: a) ☒ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of the restriction in Paper No. 12, mailed November 1, 2001 is acknowledged. The traversal is on the ground(s) that the recombinase cannot be made by another means such as the "totally synthetic means" stated in the restriction, and that the assay of the mutant recombinase could not be carried out by another means. It is further argued that the search for Group I would reveal the elements of Group IV. This is not found persuasive because the recombinase protein of Group IV can be made by totally synthetic means which are well known to those of skill in the art. The binding region of a recombinase can be easily identified and modified in the synthetically produced protein to produce a mutant recombinase. The method of Group I is used as a means of identifying which recombinase may be modified so as to alter its activity on it's natural substrate. Such an assay is presented in Lee et al. where the binding activity of mutant and wild type recombinases on mutant and wild type recombination sites are tested in an electrophoretic mobility shift assay. Thus one of ordinary skill in the art would know how to make and identify a mutant recombinase which would have altered binding to the "natural substrate" or to a modified substrate. Regarding the search, since the two Groups are classified in different subclasses, a separate search is required. Thus, a since a separate search is necessary, the argument that a search of Group I would reveal all of the elements of Group IV does not apply. The arguments are therefore not found convincing.

The requirement is still deemed proper and is therefore made FINAL.

pdk 2/25/02

2. Claims 50-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-VII, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Drawings

3. The drawings as submitted on April 6, 2000, have been approved by the draftsman.

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825)

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned.

Applicant is requested to return a copy of the attached CRF Diskette Problem Report with the reply.

Claim Objections

5. Claim 37 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 37 depends from claim 36, which depends from claim 24. Claim 37 recites "the first and second recombination sites are variant recombination sites recognized by the variant recombinase". Claim 24 states that the "variant recombinase mediates recombination between the first and second recombination sites". The variant recombinase must therefore "recognize" "the first and second recombination sites".

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: In section "(a)" the elements of the recombinase and the substrate "recombination sites" are recited as being brought into contact, and then in section "(b)" a determination is made to see if recombination has occurred. Nowhere does the claim state that the "mutant recombinase" of section "(a)" acted on the substrate to produce a recombination of the stated substrate "recombination sites". It is therefore unclear that the "mutant recombinase" has acted to produce the stated "recombination between" the substrate recombination sites.

9. Claim 2 recites "compatibility sequences". No definition is provided in the claims or specification as to what is meant by "compatibility sequences". It appears that the "compatibility sequences" may in fact be the "recombination sites" from the language of the claim, but it is also implied that the "compatibility sequences" are in fact different, since the preamble states "recognition sequences and compatibility sequences", implying that they are distinct and unique entities. For the purposes of examination, it is assumed that the "compatibility sequences" are comprised in the recombination sites.

10. Claim 3 recites the term "to a significant extent" which is a relative term which renders the claim indefinite. The term "to a significant extent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

11. Claim 24 recites a "first recombination site" and a "second recombination site". These terms appear to be used to describe a new set of recombination sites which are associated with a newly claimed "first DNA" and "second DNA", but claim 24 depends from claim 1 which has previously defined a "first recombination site" and a "second recombination site" which are associated with a "first nucleic acid" and a "second nucleic acid". The association of these previously defined elements as part of distinct newly claimed entities, a "first" and "second DNA", has produced a confusion in the meaning of the claim. The claim is therefore vague and indefinite. For the purposes of examination, it is assumed that the "first recombination site" and "second recombination site" as claimed in claim 24 are one and the same as the "first recombination site" and "second recombination site" of claim 1.

12. Claim 29 recites a "fourth DNA". There is no preceding claimed "third DNA" element, making the introduction of the "fourth DNA" element at this point in the claim structure confusing. The claim is therefore vague and indefinite.

13. Claim 29 recites a "third recombination site". This term appears to be used to describe a new recombination site which is associated with a newly claimed "fourth DNA", but claim 29 depends ultimately from claim 1 which has previously defined a "third recombination site" which is associated with a "second nucleic acid". The association of this previously defined element which is part of a new and distinct entity; a "second DNA", has produced a confusion in the meaning of the claim. The claim is therefore vague and indefinite. For the purposes of

examination, it is assumed that the "third recombination site" as claimed in claim 29 is one and the same as the "third recombination site" of claim 1.

14. Claim 30 recites at lines 3-4 "the second and third recombination sites are recombination sites recognized by wild type recombinase". Claim 30 ultimately depends from claim 1. There is a direct contradiction to the definition provided by claim 1 which states "recombination between the first and second recombination sites indicates that the mutant recombinase is a variant recombinase". Therefore, a recombinase which recognizes the second recombination site is a mutant, variant recombinase, not a wild type recombinase. This internal inconsistency makes claim 30 vague and indefinite.

15. Claim 31 recites the recombination of the first, second and third recombination sites by contacting the first, second and third recombination sites with wild type recombinase. By definition in claim 1 any recombinase which acts on the first and second recombination sites is a mutant, variant recombinase. This internal inconsistency makes the claim vague and indefinite.

16. Claim 31 recites the limitation "prior to contacting the variant recombinase with the first second and third recombination sites" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 36 recites the limitation "the third DNA" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1-4, 21, 24-25, 33-35, 40 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by McCormick et al.

McCormick et al. taught (see especially the summary, introduction, materials and methods, pages 204-206 and the figures) a method to identify a mutant recombinase, where the mutant recombinase is tested for activity on wild type and mutant recombination sites. The mutant recombination sites (first and second sites) are on a first nucleic acid and the wild type recombination sites (third and fourth) are on a second nucleic acid. The wild type and mutant recombination sites are linked to selectable markers. The mutant recombinase has greater activity with the mutant recombination sites than with the wild type recombination sites, and the wild type recombinase has lowered activity with the mutant recombination sites. In a single experiment to test recombination activity, the mutant recombination sites are identical, and the wild type recombination sites are identical. The first and second nucleic acids contain structural genes. The recombination occurs in a bacterial cell.

20. Claims 1-4, 23-25 and 48 rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al.

Lee et al. taught (see especially the abstract, introduction, materials and methods and the figures) a method to identify a mutant recombinase, where the mutant recombinase is tested for activity on wild type and mutant recombination sites. The mutant recombination sites (first and second sites) are on a first nucleic acid and the wild type recombination sites (third and fourth) are on a second nucleic acid. The wild type and mutant recombination sites comprise selectable markers. The mutant recombinase has greater activity with the mutant recombination sites than with the wild type recombination sites, and the wild type recombinase has lowered activity with the mutant recombination sites. In a single experiment to test recombination activity, the mutant recombination sites are identical, and the wild type recombination sites are identical. The recombination reaction is performed *in vitro*.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of McCormick et al. or Lee et al. in view of US 5,677,177.

The claims are drawn to a method to identify a mutant recombinase, where the mutant recombinase is tested for activity on wild type and mutant recombination sites. The mutant recombination sites (first and second sites) are on a first nucleic acid and the wild type recombination sites (third and fourth) are on a second nucleic acid. The wild type and mutant recombination sites are linked to selectable markers. The mutant recombinase has greater activity with the mutant recombination sites than with the wild type recombination sites, and the wild type recombinase has lowered activity with the mutant recombination sites. In a single experiment to test recombination activity, the mutant recombination sites are identical, and the wild type recombination sites are identical. The first and second nucleic acids contain structural genes. The recombination occurs in a bacterial cell. The recombination of the first and second recombination sites alters expression of the first reporter and recombination between the third and fourth recombination sites alters expression of the second reporter. The reporter gene expression may be activated or inactivated by the removal of a spacer in, or near the reporter which blocks expression of the reporter gene. The reporter gene may be activated or inactivated by an inversion of part or all of the reporter gene. The reporter gene may be excised from the construct. The first and second nucleic acid sequences may be connected by a preselected DNA segment. The recombination reaction may occur *in vitro* or may occur in a cell which may be in a prokaryotic cell or a eukaryote cell. The eukaryotic cell may be in a plant or a mammal.

Each of McCormick et al. or Lee et al. taught the invention as described above in the rejections under 35 USC 102.

Each of McCormick et al. or Lee et al. did not teach that the first and second nucleic acids may be linked by a DNA segment, nor the deletion or excision of the reporters or spacers, nor inversion of the reporters to switch on or switch off expression of the reporters. Also not taught was the performance of the method in a eukaryotic cell.

US 5,677,177 taught (see especially the abstract, Brief Description, figures and columns 3-8) the well known use of a recombinase to insert, invert and delete a sequence in a construct to inactivate or activate a desired gene sequence, such as a reporter, in a mammalian cell, where the cell may be in a mammal.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of each of McCormick et al. or Lee et al. with US 5,677,177 to produce the instant invention because McCormick et al. taught the use of the method of identification of mutant recombinases in a model system, where the teachings would apply to other recombination methods, and Lee et al. taught the identification of mutant recombinases to use the recombinases in methods of modification of HIV-1, for treatment of disease in humans. US 5,677,177 taught the general utility of use of a recombinase to insert, invert and delete sequences in a construct to inactivate or activate a desired gene sequence, such as a reporter in a mammalian cell with specific applicability to any recombination method.

One of ordinary skill in the art would have been motivated to combine the teachings of each of McCormick et al. or Lee et al. with US 5,677,177 to produce the instant invention because US 5,677,177 taught the desirable and beneficial use of a recombinase to insert, invert

and delete sequences in a construct to inactivate or activate a desired gene sequence, such as a reporter in a mammalian cell, where the cell may be in a mammal. The deleting, inserting and inverting activity of recombinases is well known, and US 5,677,177 taught this specific, desirable and beneficial use of a recombinase in any method involving the use of a recombinase where activation or inactivation of a gene is desired. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of McCormick et al. or Lee et al. with US 5,677,177.

Conclusion

23. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can

be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

February 25, 2002